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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/728,041	12/03/2003	Samuel J. Danishefsky	2003080-0142 (SK-893-B-US	4230

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EXAMINER	
CANELLA, KAREN A	

ART UNIT	PAPER NUMBER
1643	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/728,041	DANISHEFSKY ET AL.	
	Examiner	Art Unit	
	Karen A. Canella	1643	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on _____.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☐ Claim(s) 1-58 is/are pending in the application.

4a) Of the above claim(s) 48-58 is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☐ Claim(s) 1-47 is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date 1/31/05 1/12/04.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Acknowledgment is made of applicant election of Group I, claims 1-47. After review of the record, the requirement that Applicant identify the elected species in the notice, mailed March 26, 2007 is hereby withdrawn as there was no election of species requirement in the September 29, 2006 Restriction Requirement.

Claims 1-58 are pending. Clams 48-58, drawn to non-elected inventions, are withdrawn from consideration. Claims 1-47 are examined on the merits.

Priority

Applicant's claim for the benefit of a prior-filed application under 35 U.S.C. 119(e) or under 35 U.S.C. 120, 121, or 365(c) is acknowledged. Applicant has not complied with one or more conditions for receiving the benefit of an earlier filing date under 35 U.S.C. 119(e) as follows:

Acknowledgement is made of applicant's claim to an earlier effective filing date via provisional application 60/150,088, filed August 20, 1999. After review of the '088 application it was concluded that it fails to provide support for the instant claims. The '088 application provide a written description of the synthesis of the fucosyl GM1 KLH conjugate (page 16) only. The provisional make no mention of a glycopeptide comprising a peptide backbone, or a glycopeptide which is multi-antigenic by virtue of being a cluster antigen or incorporation of distinct carbohydrate antigens into the same glycopeptide. Accordingly the instant claims are given priority to the earliest application that provide an adequate written description of the instant claimed constructs and methods of making said constructs which is 09/641,742, filed August 18, 2000.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 5-7 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 5 and 8 recite 'wherein each occurrence of L1 is a natural amino acid side chain'. It is unclear how L1 can be a natural amino acid side chain as it is required to be covalently linked to the "A" carbohydrate moiety which is not part of a natural amino acid

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-3, 5-19, 21-30, 32-47 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for multiantigenic constructs and methods of making said constructs, wherein the constructs are Globo-H, fucosyl GM1, KH-1, gycophorin, N3, Tn, TF, STn, (2,3)ST, (2,6)STn, GB3, LeY and LeX does not reasonably provide enablement for the multitude of variant structures and methods of making said structures encompassed by the differing "A" substituents as listed in claims 1 and 36 and the structure of claim 20.. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims. The factors considered when determining if the disclosure satisfies the enablement requirement and whether any necessary experimentation is undue include, but are not limited to: 1) nature of the invention, 2) state of the prior art, 3) relative skill of those in the art, 4) level of predictability in the art, 5) existence of working examples, 6) breadth of claims, 7) amount of direction or guidance by the inventor, and 8) quantity of experimentation needed to make or use the invention. In re wands, 858 F.2d 731, 737.8 USPQ2d 1400, 1404 (Fed. Cir. 1988).

The instant specification provides for the synthesis of multiantigenic-carbohydrate antigens, such as those in cancer cells, on a peptide backbone. The specification teach that these carbohydrate domains are useful in evoking an immune response in cancer patients. The specification provides no teachings as to how to use a glycopeptide construct that is not a domain

which would evoke a efficacious immune response in a patient. The specification does not identify an antigenic structure that comprises "furanose moieties" of fluorine atoms (recited in claims 1 and 36), or a pattern of ring substituents having R groups that differ from the R groups on carbohydrates found on cancer cells.

The instant claims are drawn in part to a carbohydrate determinate within which the values of "g" plus "i" is 1 or 2, the value of "d" plus "f" is one or two, and the value of "b" plus "c" is one or two. Claims 56 and 76 also state the bracketed structures can encompass furanose as well as pyranose moieties. In the event that "g" plus "i" is 1 or "d" plus "f" is one, or "b" plus "c" is one, the ring structures will be furanose moieties. The specification teaches that Globo-H, fucosyl GM1, KH-1, glycophorin, STN, LeY, N3, Tn, 2-6STn, (2,3)ST and TF are cancer carbohydrate antigens which are over-expressed at the surface of malignant cells in a variety of cancers (page 2, lines 4-8). All of the aforesaid cancer antigens are pyranose moieties. The specification does not teach cancer carbohydrate antigens which comprise furanose sugar moieties rather than the pyranose sugar moieties. While sugars lacking one carbon from those found in Globo-H, fucosyl GM1, KH-1, glycophorin, STN, LeY, N3, Tn, 2-6STn, (2,3)ST and TF are known in the art (for example, the abstract of Severin et al, Biokhimiya (Moscow), 1973, Vol. 38, pp. 583-588), there are no cancer associated carbohydrates recognized in the art. The review article of Garg et al (Advances in Carbohydrate Chemistry and Biochemistry, 1994, Vol. 50, pp. 277-310,reference of the IDS filed 1/12/2004) indicates in Table I, page 278, the amino acid-carbohydrate residue lineage found in mammals. It is noted that none of the carbohydrate residues would have a furanose moiety. Further, the specification has failed to provide a synthetic methodology for a furanose polysaccharide derivative which would be required for reaction to the n-alkenyl group (section (a) of claim 61). It is concluded that one of skill in the art would be subject to undue experimentation is order to make a and use glycopeptide comprising the alkenyl glycoside structure and one of skill in the art would be subjected to undue experimentation without reasonable expectation of success in using said furanose polysaccharide without teachings of a type of cancer or pathological state which would be commensurate with the over-expression of a furanose polysaccharide on the cell surface.

Further, the specification does not teach how to synthesize the molecules which are not the carbohydrate domains of Globo-H, fucosyl GM1, KH-1, glycophorin, STN, Ley, N3, Tn,

2,6Tn, 2,3ST or TF. There is no nexus between the synthesis of the aforesaid molecules and the synthetic approach to an antigen structure that differs in the number of pyranose rings , and the substitution pattern on the pyranose rings because the Globo-H, fucosyl GM1, KH-1, glycophorin, STN, Ley, N3, Tn, 2,6Tn, 2,3ST or TF molecules are complex and governed by a multitude of physical interactions based on the accumulation and positioning of the various electron withdrawing groups of the substituents encompassed by the claims. The presence of differing functional groups, heteroatoms, such as Fluorine in the instant case, and three dimensional configurations require different considerations as to protecting groups, and reactivity manifest in different synthetic strategies (Sierra and de la Torre, Angewandte Chemie, 2000, Vol. 39, pp. 1538-1559, especially pages 1544-1546, "Troublesome Protecting Groups"). Chemical structure heterogeneity including the presence of different heteroatoms or aryl groups on different three dimensional structures can radically alter the reactivity of any other atom within a molecule through inductive effects (page 1545, second column, lines 2-6 of the second full paragraph and lines 4-7 of the third full paragraph), resonance effects, acidity, basicity, steric hindrance (page 1552-1554), strain (page 1554-1557) or transition state crowding (page 1545, second column, second full paragraph, lines 2-6,page 1546, second column, first full paragraph) and therefore can radically influence the reactivity with any given reagent contacted thereto. Sierra and de la Torre teach that a well-testing transformation can fail for complex reasons (Sierra and de la Torre, ibid, page 1540, first column, lines 9-11, page 1541, first column, lines 33-37, under the heading "Working Models that do not Work", page 1542, first column, lines 15-17, even when supported by molecular mechanics calculations (page 1542, first column, lines 6-9) and what is seen as an innocuous alteration can cause a failure in a synthetic step (page 1542, second column, lines 9-12). Sierra and de la Torre teach that the presence of remote substitutions has unexpected influence over a chemical step (pages 1546-1548, under the heading "The Unexpected Influence of Remote Substituents") Sierra and de la Torre state that "As the complexity of intermediates increases, the number of variables involved in a simple transformation grow exponentially making predictions about the outcome of any given synthetic step on a highly functionalized intermediate, unreliable (page 1548, second column, lines 5-8 of the second full paragraph, page 1550, second column, lines 1-9 under the heading "The Trivial Functional Group Transformation"). Sierra and de la Torre conclude that the lack of

predictability in so many cases and the very empirical nature of synthetic organic chemistry implies that the science is not fully developed (page 1548, second column, lines 13-16 of the second full paragraph). Sierra and de la Torre state that alternate routes can then be devised which circumvent a failed transformation (page1548, second column, lines 10-13 of the second full paragraph). However, the sum total effort of designing and redesigning represents undue experimentation to one of skill in the art, exemplified by Sierra and de la Torre as "the amount of effort devoted to simple transformations is still quite enormous" (page 1557, first column, lines 15-18). It is noted that the multiantigenic glycopeptides encompassed by the claims are densely multifunctionalized agents. Thus, the specification teaches how to make glycopeptides comprising Globo-H, fucosyl GM1, KH-1, glycophorin, STN, Ley, N3, Tn, 2,6Tn, 2,3ST or TF, but the scope of the instant claims comprises a greater degree of variance with respect to the carbohydrate moieties and the means to make such moieties and the means to use said moieties are unknown. therefore one of skill in the art would be subject to undue experimentation in order to make and use all the structures within the scope of the claims.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1, 2, 4-6, 9-13, 21-28, 47 are rejected under 35 U.S.C. 102(b) as being anticipated by Danishefsky (WO98/46246, reference of the IDS filed January 12, 2004).

Danishefsky et al disclose a composition comprising a clustered O-linked glycopeptidic moiety wherein the glycopeptide incorporates glycosyl units with clustered ST epitopes (page16, line 32 to page 17, line 2) in addition to glycopeptides wherein the carbohydrate domains are MBr1 (Globo-H), truncated MBr1 epitope (pentasaccharide), truncated MBr1 epitope (tetrasaccharide), SSEA-3 antigen, LeY and GM1 (page 17, lines 3-12), constructs comprising "linkers" (Figure 20C) which fulfill the specific embodiment of claims 11 and 12 in that the "linker" of '246 is a substituted C2 alkylidene chain where the hydrogen is replaced by

$NR^{Z1}CONR^{Z2}$ wherein R^{Z1} is a peptidyl moiety and R^{Z2} is the alkyl C2 moiety Figure 20C7; constructs in which RX1 is an acyl moiety and an amino acid residue (Figure 2B), linkers of claims 21 and 22 (Figure 19B), crosslinkers having the structure of claim 23 (Figure 21C), conjugation to the immunogenic carriers of BSA and KLH (Figure 21D), the lipid immunogenic carrier of claim 28 (Figure 20C), attachment of the glycopeptide antigen to the lipopeptide carrier PamCys (page 62, lines 30-31 which fulfills the embodiment of claim 30.) and methods of making the disclosed structures and conjugates (Examples 1-47)which fulfill the embodiments of claim 36. Danishefsky et al disclose the carrier protein is bovine serum albumin, poly-lysine or KLH and the co-administering of an immunological adjuvant such as bacteria or liposomes, Salmonella minnesota cells, bacille Calmette-Guerin or QS21 (page 12, lines 8-18 and 27-31) . Danishefsky et al disclose the attachment of the glycopeptide antigen to the lipopeptide carrier PamCys (page 62, lines 30-31).

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned

with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 1, 3-6, 9-35, 37-47 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 56, 58-62, 65-67, 69-76, 78-81, 84-86, 88-98 of copending Application No. 09/641,742. Although the conflicting claims are not identical, they are not patentably distinct from each other because the claims of the '742 application anticipate the constructs with a spacer, because the limitations claimed in claim 62 of the reference patent fulfill the instant limitations of claims 11 and 12 with regard to a spacer. Further claim 74 of the reference application also indicate that "t is 1-8" methylene groups which also fulfils the instant limitation of claims 11 and 12. Further, claim 74 of the reference application specifies that "n is 1-8" which fulfills the instant limitations for claims 5-7.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Claims 1, 3-7, 9-22, 24, 31-33, 35, 37, 39, 40, 43-47are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 118-129, 132-137, 138-146, 148-168 of copending Application No. 10/209,618. Although the conflicting claims are not identical, they are not patentably distinct from each other because the claims of the '618 application anticipate the constructs with a spacer, because the limitations claimed in claim 128, 129, 140, 151 and 152 of the reference patent fulfill the instant limitations of claims 11 and 12 with regard to a spacer and in particular, claim 140 includes "linear or branched chain alkly". Further claims 132 and 133 of the reference application also indicate that "n is 0-9" and "n is 3"methylene groups which also fulfils the instant limitation of claims 5-7. Claims 154-159 of the reference patent are product by process claims and anticipate the instant invention through identity of the species in claim 118 of the reference application.

All claims are rejected.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Karen A. Canella whose telephone number is (571)272-0828. The examiner can normally be reached on 10-6:30 M-F.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Larry Helms can be reached on (571)272-0832. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Karen A. Canella/
Ph.D., Primary Examiner
Art Unit 1643